SA-PO146

Analyses from a Phase 2 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Type 1 Diabetes: The PHOENIX Study

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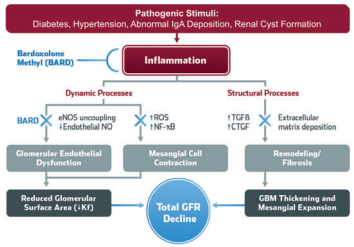
BACKGROUND AND RATIONALE

CKD Associated with Type 1 Diabetes

- Type 1 diabetes (T1D) affects an estimated 1.25 million people in the US[1]
- CKD affects approximately 10-20% of patients with T1D or roughly 150,000 people in the US[2]
- In patients with T1D CKD, hyperglycemia due to poor glycemic control can initiate pathological pathways that initiate fibrosis and loss of kidney function[3]



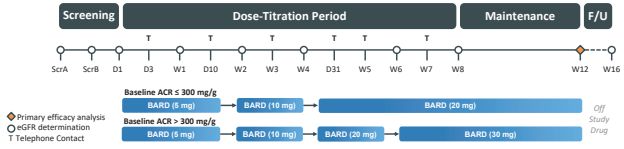
Through induction of Nrf2 and suppression of NF-κB, Bard targets common pro-inflammatory and fibrotic pathways that contribute to GFR loss in CKD[4]

- Despite diverse etiologies, inflammation is a common mechanism underlying the development and progression of chronic kidney disease (CKD)[5]
- Bard improves kidney function by increasing filtration surface area and by reducing inflammation, remodeling, and fibrosis in multiple models of CKD and AKI[6-8]
- In 11 clinical trials that enrolled over 2,600 patients, Bard increased eGFR[9-12]
  - eGFR increases verified as true improvement in GFR by inulin clearance[13]
  - eGFR improvements durable for up to two years and partially retained after drug withdrawal[10,11]
  - Bard reduced risk of kidney failure outcomes in patients with type 2 diabetes and stage 4 CKD in BEACON[12]

Phase 2 PHOENIX trial was initiated to determine whether Bard improves kidney function in patients with T1D CKD

PHOENIX STUDY DESIGN

- Phase 2, open-label, multi-center, US-only trial (NCT03366337)
  - Four separate cohorts of patients with ADPKD, IgAN, T1D CKD, or FSGS
  - Targeted enrollment of 25 to 30 patients per cohort
- Primary endpoint: change in eGFR from baseline at Week 12
- Key eligibility: eGFR ≥ 30 to ≤ 90 mL/min/1.73 m^2; 18-65 years old; diagnosis of T1D confirmed by fasting C-peptide



BASELINE CHARACTERISTICS

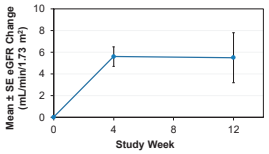
- Enrolled 28 patients and 24 (86%) completed treatment through Week 12
- Historical eGFR data from 3 years prior to enrollment collected for 22/28 patients
- Average annual loss of eGFR of 1.9 mL/min prior to study entry

Characteristic	Total (N=28)
Age, years (mean ± SD)	49 ± 10
Baseline eGFR, ml/min (mean ± SD)	68 ± 17
Baseline ACR, mg/g (geometric mean)	30.9
ACR ≤ 300 mg/g (n,%)	21 (75%)
ACR > 300 mg/g (n,%)	7 (25%)
Receiving ACEi or ARB (n,%)	19 (68%)
Average yearly historical eGFR decline (mL/min, n=22)	1.9

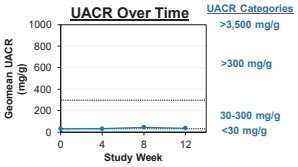
EFFICACY: CHANGE IN eGFR

- Bard treatment resulted in significant eGFR increase of 5.5 mL/min/1.73 m^2 at Week 12
- Increase represents recovery of ~3 prior years of loss based on historical data
- Lower treatment effect and higher variability in subset of patients with near-normal eGFR at baseline (≥80 mL/min; n=8/28)

	Change from Baseline in eGFR	
	WK4	WK12
Mean ± SE	5.6 ± 0.9	5.5 ± 2.3
p-value	p<0.001	p=0.02



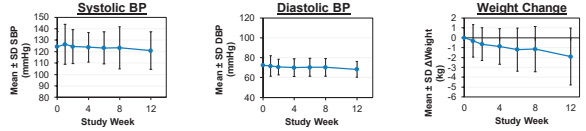
URINARY ALBUMIN TO CREATININE RATIO



- Patients had normal to near-normal levels of urinary albumin at baseline
- Bard treatment did not change urinary albumin despite the increase in eGFR

VITAL SIGNS

- Blood pressure (BP) stable and within normal limits during treatment
- No evidence of overt fluid retention and no significant weight increases during study
- Consistent with prior studies, slight decreases in weight observed[14]



SAFETY: ADVERSE EVENTS

Preferred Term	Total N=28
Muscle spasms	9 (32%)
Headache	6 (21%)
Nausea	5 (18%)
Fatigue	4 (14%)
Arthralgia	3 (11%)
Hepatic enzyme increased	3 (11%)
Hypoglycaemia	3 (11%)
Upper respiratory tract infection	3 (11%)

*AEs reported in >10% patients

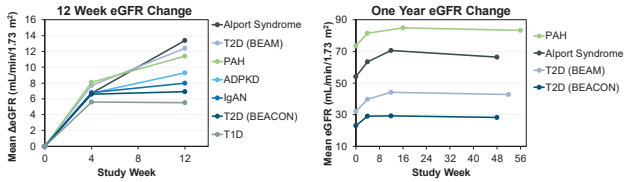
- No treatment-related serious adverse events
- 2 patients (7%) discontinued treatment prematurely due to Bard-related AE (constipation, dizziness)
- AEs to date have been generally mild to moderate in intensity
- Most commonly reported AE was muscle spasms, which are associated with reductions in creatine kinase
- Transaminase increases are pharmacological effect of Nrf2 activation and not associated with liver injury

CONCLUSION

- Bardoxolone methyl significantly improved eGFR (+5.5 mL/min/1.73 m^2) in patients with T1D CKD
- No change in albuminuria
- Bard was well-tolerated without any drug-related SAEs, changes in blood pressure, or evidence of fluid overload
- Data suggest that long-term eGFR improvements and retained eGFR benefit observed in other forms of CKD may translate to patients with T1D CKD

FUTURE DIRECTIONS

- Increases in eGFR observed in six distinct patient populations following Bard treatment
- Long-term eGFR increases of one to two years observed in three patient populations
  - eGFR improvement post-withdrawal observed in two patient populations
  - Acute changes in eGFR correlate with durable response and retained eGFR benefit
- Planning to pursue T1D CKD as commercial indication
- Bard is also currently being studied in:
  - CARDINAL: Phase 2/3 study in patients with Alport syndrome
  - AYAME: Phase 3 outcomes study in Japanese patients with diabetic CKD



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DISCLOSURES

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MPC and CJM are employees of Reata Pharmaceuticals.